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Diurnal Cortisol Interacts With Stressful Events to Prospectively Predict Depressive Symptoms in Adolescent Girls

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A B S T R A C T

Purpose: The aim of present study was to test the diathesis-stress model of depression using baseline cortisol, prospective assessment of depression symptoms, and stressful life events.
Methods: The sample consisted of 527 adolescent girls aged 13.5–15.5 years without major depressive disorder. At baseline, saliva samples were collected at waking, 30 minutes after waking, and 8 P.M. on 3 consecutive days. Diurnal cortisol was indexed by cortisol awakening response (CAR) and area under the curve with respect to ground (AUCg). Stressful events during the preceding interval and current depressive symptoms were assessed 18 months following baseline.
Results: Stressful events and the interaction of CAR or AUCg with stressful events predicted depressive symptoms at 18 months, even after controlling for baseline depressive symptoms. Specifically, in the face of high levels of stress, baseline blunted CAR or smaller AUCg were associated with future depressive symptoms. This was more apparent for CAR than AUCg. The effect was reversed at low levels of stress, with heightened CAR associated with more severe depressive symptoms.
Conclusions: Blunted CAR and less daily cortisol output at baseline appear to accentuate the depressogenic effects of stressful events after 18 months, consistent with the diathesis-stress model of hypothalamic-pituitary-adrenal axis function in depression.

IMPLICATIONS AND CONTRIBUTION

Findings from the present study imply that blunted cortisol awakening response and less daily cortisol output are associated with the development of depressive symptoms after experiencing stressful events in adolescent girls. Findings contribute to current understanding of biological risk factors for major depressive disorder in early adolescence.

Major depressive disorder (MDD) is a serious mental health problem in adolescent girls, who face prevalence rates more than double that of boys (10.7% vs. 4.6%, respectively) [1], making it imperative to identify factors that put them at risk. Stress is a well-documented risk factor for depressive disorders and symptoms, including among adolescent girls [2–6]. Numerous studies have documented the onset of MDD or depressive symptoms during adolescence following life stress [2–6]. However, other studies reported no such effect [7]. Hence, stress by itself may be necessary but not sufficient for youth to develop MDD or depressive symptoms [8]. Rather, certain youth may be at increased risk of developing the disorder in the face of stress [8]. Indeed, the diathesis-stress model of depression posits that the influences of stress on depression partly depend on individuals' sensitive to the deleterious effect of stress [9].

A number of biological factors have been investigated as potential markers of stress sensitivity (i.e., diatheses), and some of them have been linked to MDD. One such factor is altered hypothalamic-pituitary-adrenal (HPA) axis, which is reflected in

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dysregulated diurnal cortisol. The HPA axis is a neuroendocrine system and one of the most fundamental physiological systems involved in responding to stress [10]. Importantly, the HPA axis is responsible for mobilizing energy resources within the body and maintaining individuals' homeostasis during the stress response [10].

In an early attempt to test the diathesis-stress model of depression in adolescents, researchers examined whether dysregulated diurnal cortisol alone could be a potential diathesis associated with MDD, even without regard to stress. Evidence from prospective studies has shown that several indices of diurnal cortisol were associated with MDD onset and symptom acceleration in adolescents. For example, increased levels of morning cortisol alone were reported to predict MDD onset [11–13]. Recent studies have reported that one index of diurnal cortisol in particular, the cortisol awakening response (CAR), was a significant prospective predictor of the onset of MDD across a 2.5-year follow-up period in older adolescents [14,15]. Specifically, every standard deviation increase in CAR doubled the risk for MDD [15]. However, contradictory findings were also reported in two studies, indicating CAR did not prospectively predict MDD onset in youth [8,16].

A second index of diurnal cortisol, cortisol area under the curve with respect to ground (AUCg), has received increasing attention in research for three reasons [8,17]. First, distinct from CAR, AUCg represents total volume of daily cortisol output [17,18]. The formula used to calculate AUCg incorporates multiple time points, daily cortisol fluctuation, and total volume of cortisol circulation [8,18]. As such, AUCg may provide a more comprehensive picture regarding basal activity of the HPA axis. Second, among the diurnal cortisol indicators studied in the literature (e.g., CAR, diurnal slope, and AUCg), AUCg is evidenced to be the most stable index, demonstrating the least day-to-day variability (followed by diurnal slope and CAR) [19–21]. The stability of AUCg makes it a good candidate to represent individuals' trait-like characteristics. Third, AUCg has been associated with the development of MDD. Evidence from a prospective study suggested that higher levels of daily cortisol tripled risk for a major affective disorder in adolescents [22]. However, Vrshek-Schallhorn et al. [15] reported no such effect of AUCg, indicating AUCg alone did not predict MDD onset.

Direct tests of the diathesis-stress model of depression require assessments of depression, diurnal cortisol, and stressful events in a prospective design. Such studies of adolescents are rare. So far, two studies using naturalistic stressful events have reported mixed findings [8,15]. In both studies, results showed no interaction effect between CAR and stressful events on MDD onset [8,15]. Only one study revealed high levels of AUCg interacted with naturally occurring stressful events to predict MDD onset in adolescent girls with no history of psychopathology [8], whereas the other study did not report the interaction between AUCg and stressful events [15]. Thus, support for the diathesis-stress model of depression in adolescence is mixed, possibly due to inconsistency in measuring cortisol (e.g., in the context of stress [8,15] vs. alone without regard to stress [11–13]) or stressful events (e.g., chronic stress over a year [15] vs. self-reported stress over a few years [8]).

The aim of the present study was to directly test the diathesis-stress model of depression using a larger sample of adolescent girls with no history of psychopathology and an objective assessment of stressful events. We assessed whether the interaction between baseline diurnal cortisol and intervening stressful events would prospectively predict self-reported depressive symptoms 18 months later.

Methods

Participants

Adolescent girls (N = 550) aged 13.5–15.5 years (M_{age} = 14.39, standard deviation = .62) and one of their biological parents were recruited for the Adolescent Development of Emotions and Personality Traits project. Participants were mostly recruited using phone lists, and all families were financially compensated for their participation [23]. Inclusion criteria of the Adolescent Development of Emotions and Personality Traits project were ability to read and understand English questionnaires and participation of at least one biological parent [23]. To ensure a healthy adolescent sample, exclusion criteria included lifetime history of MDD, dysthymia, or intellectual disabilities, habitual smoking, and medication use (i.e., anti-inflammatory drugs) or disease that might potentially influence the activity of the HPA axis [23]. The absence of a lifetime history of MDD or dysthymia at the baseline assessment was confirmed by a diagnostic interview using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (KSADS) [24]. Diagnostic interviews were conducted by experienced interviewers under supervision of clinical psychologists (R.K., G.P., and D.K.) [23]. No adolescent in the sample was diagnosed with MDD based on KSADS. In total, 23 adolescent participants were deemed as outliers (see Statistical analyses for details of outlier analysis), leaving a final sample of 527 adolescents. Racial and ethnic composition of the final sample was 81.6% non-Hispanic white. The study was approved by the Stony Brook University Institutional Review Board. Informed parental consent and adolescent assent were obtained.

Clinical assessments

Inventory of Depression and Anxiety Symptoms (IDAS-II) [25] General Depression scale was used to assess adolescents' depressive symptoms at baseline and 18 months. The IDAS-II is a 99-item self-report measure with 18 specific scales plus General Depression. Each symptom in the scale was rated on a five-point Likert scale from 1 (not at all) to 5 (extremely) [25]. The scale had excellent internal consistency at baseline and 18 months (α's = .89 and .91, respectively).

The Stressful Life Events Schedule [26] was used to assess for intervening stressful events (e.g., death of family or friends) at 9 months and 18 months. The Stressful Life Events Schedule is an interview instrument, which was designed to examine the relationship between stress and depression in children and adolescents [26]. At each follow-up assessment, adolescents were interviewed about their stressful events that had happened during the preceding interval. Consistent with administration guidelines, events were rated by consensus of trained interviewers on a four-point scale (1, 2, 3, and 4; "objective threat ratings") [26]. A total score of stressful events was calculated by squaring objective threat rating for each event and summing the squared ratings [26].

Biological assessments

Saliva samples collection and cortisol assay. Adolescent participants collected saliva samples three times a day (upon waking,

30 minutes after waking, and at 8 P.M.) over 3 consecutive days using Salivette sampling devices (Salimetrics, Inc.) [23]. Participants were asked not to eat or drink before collecting each sample [27], and to record waking time, each saliva sample collection time, as well as any illness symptoms on a given sampling day in a diary [23]. Sample collection times were then verified by an objective time recording device, MEMSCap. This device recorded the time when each saliva swab was taken from a storage container.

The saliva samples were stored in the freezer at home until they were delivered to the laboratory and placed in a −80°C freezer [23]. Experimenters followed standard laboratory safety procedures for handling saliva samples. Saliva samples were assayed in duplicate for cortisol, using a time-resolved immunoassay with fluorescence detection (DELFIA). An average coefficient of variation (CV) for each sample was calculated. The samples were reanalyzed when CV values were greater than 12% and cortisol values were greater than 5 nmol/L, as well as any cortisol values $\geq$ 100 nmol/L. The average of the duplicate values was used for the subsequent analyses.

Body mass index and pubertal stage. Self-reported height and weight were used to calculate adolescents' body mass index (BMI). Two scales were used to assess pubertal stage in adolescents. The first measure was Pubertal Development Scale [28], which has five items assessing five aspects of growth, including height, body hair, skin changes, and breast development, and menarche. The first four items are assessed on a four-point Likert scale ranging from 1 (not yet started) to 4 (seems complete), and the last one was assessed on a binary scale (yes or no). The second measure was the photographic representations of Tanner's five stages of pubertal development [29]. Adolescents were asked to rate pubic hair and breast development based on the pictorial representations ranging from "prepubertal" to "fully matured". The ratings from both measures were summed and standardized into z-scores separately. A composite index of pubertal stage was then calculated by summing the two z-scores.

Procedure

During the baseline laboratory visit, adolescent participants completed the KSADS, IDAS-II, as well as the assessments of BMI and pubertal stage [23]. Participated parents completed demographic information. Before the visit, a saliva sample collection kit with detailed instructions (verbal, written, and video) on how to collect saliva samples, keep a diary, and store saliva samples at home was mailed to each family. Adherence to instructions was checked during the baseline visit (diary and MEMS data). If nonadherence presented between the two methods, adolescents were given additional training and asked to retake saliva samples in days after the visit. Participants were interviewed for stressful life events at follow-up assessments. The attrition rate with respect to the outcome (i.e., depressive symptoms at 18 months) was 6.8%.

Statistical analyses

Before testing hypotheses, cortisol data were inspected for outliers [23]. Four criteria were used to identify outliers, namely, (1) standardized cortisol values were bigger than three standard deviations from the mean; (2) adolescent participants were ill on a given sampling day (e.g., any illness symptoms indicated in the diary); (3) blood contamination (e.g., from cuts in the mouth); and (4) saliva samples deemed to be collected nonadherent to sampling instructions (i.e., participants ate or drank before collecting saliva samples or saliva samples were collected outside the instructed time) [23]. In most cases, only single sample was deemed outliers, and the remaining samples for that person were retained. However, there were 23 adolescents for whom all their saliva samples were deemed outliers (e.g., participant illness across the 3 days) and were removed from subsequent analyses.

Three diurnal cortisol indices, AUCg [18], CAR [30], and diurnal slope [20], were calculated. Given that the cortisol diurnal slope is a less evidenced risk factor to depression, this index was analyzed in an exploratory manner. The AUCg, which is a reflection of daily total cortisol output, was calculated with all three saliva samples using the formula described in Pruessner et al [18]. The CAR was calculated as the increase in cortisol values between waking and 30–45 minutes after awakening [30]. Cortisol diurnal slope was calculated as the slope of cortisol changes from awakening to evening [20]. Prior to analyses, cortisol indices were adjusted for any minor time difference between the corresponding sample collection times and target times [23]. Adjusted cortisol values were then averaged across three sampling days for the subsequent analyses [31].

To address the study aim, a hierarchical multiple regression analysis was performed, with 18-month depressive symptoms regressed on baseline cortisol (AUCg, CAR, or diurnal slope) and intervening stressful events entered in step 1, and the interaction of baseline cortisol and stressful events using Aiken and West's procedures entered in step 2. Covariates entered in step 1 were baseline variables, including adolescents' age, BMI, pubertal stage, and baseline depressive symptoms.

Results

Descriptive statistics for study variables are presented in Table 1. AUCg and CAR were strongly interrelated ($r = .77, p < .001$), whereas diurnal slope was negatively associated with AUCg and CAR, respectively ($rs = -.27$ and .17, respectively, $p < .001$). When entering all three cortisol indices simultaneously to predict depressive symptoms at 18 months, only AUCg significantly predicted depressive symptoms at 18 months ($\beta = -.19, p < .05$).

Results from the hierarchical multiple regression are summarized in Table 1. Briefly, baseline depressive symptoms significantly predicted depressive symptoms at 18 months ($p < .001$). CAR, AUCg, or diurnal slope did not predict depressive symptoms at 18 months, whereas stressful events did ($p < .001$). The interaction between CAR and stressful events added in step 2 significantly predicted depressive symptoms at 18 months ($\beta = -.18$, $p = .040$; region of significance of stressful events = [−24.46 to 6.00], 24.9% of the sample fell within this region). Similarly, the interaction between AUCg and stressful events added in step 2 was a significant predictor to depressive symptoms at 18 months ($\beta = -.27$, $p = .016$; region of significance of stressful events = [−8.22 to 23.22], 74.4% of the sample fell within this region). However, the interaction between stressful events and diurnal slope did not significantly predict depressive symptoms at 18 months ($\beta = .03$, $p = .698$).

Figure 1 depicts the interaction for CAR (Figure 1A) and AUCg (Figure 1B) with stressful events in predicting depressive symptoms at 18 months. Consistent across the two indices, high levels of stress plus blunted CAR or less daily cortisol output

Table 1
Adolescents' demographic, clinical characteristics, and results of predicting depressive symptoms at 18 months

Predictor	M (SD)	CAR					AUCg				
		ΔR^2	β	95% CI	*t*	*p* value	ΔR^2	β	95% CI	*t*	*p* value
Step 1		.32				<.001	.32				<.001
Constant				−12.74 to 34.57	.91	.365			−12.20 to 35.01	.95	.343
Baseline age	14.39 (.62)		.04	−.80 to 2.41	.98	.326		.04	−.71 to 2.50	1.10	.274
Baseline BMI	21.79 (4.14)		−.12	−.63 to −.12	−2.88	.004		−.12	−.63 to −.12	−2.89	.004
Baseline pubertal stage[a,b]	−.02 (1.77)		.03	−.38 to .88	.78	.438		.04	−.35 to .90	.86	.390
Baseline depression symptoms	32.75 (12.25)		.40	.33 to .49	10.05	<.001		.41	.33 to .50	10.15	<.001
Baseline cortisol[c]											
CAR[d]	8.00 (5.76)		.00	−.16 to .18	.10	.919		—	—	—	—
AUCg	120.18 (46.47)		—	—	—	—		−.05	−.04 to .01	−1.36	.175
Intervening stressful events	16.60 (14.45)		.30	.19 to .33	7.49	<.001		.30	.19 to .33	7.40	<.001
Step 2		.01				.040	.01				.016
Cortisol × stressful events	—		−.18	−.02 to −.00	−2.06	.040		−.27	−.00 to .00	−2.43	.016

AUCg = area under the curve with respect to the ground; BMI = body mass index; CI = confidence interval; CAR = cortisol awakening response; M = mean; SD = standard deviation.

[a] The descriptive statistics for each indicator on Pubertal Development Scale were as follows: M_{Height} = 3.32, $M_{Body\ Hair}$ = 3.54, $M_{Skin\ Changes}$ = 3.01, and $M_{Breast\ Development}$ = 3.03. The average age of menstruation in the present sample was 12.53 years.

[b] Pubertal stage was positively correlated with CAR ($r = .10$, $p = .027$), but not with AUCg ($r = .08$, $p = .059$), at baseline. Pubertal stage, CAR or AUCg, the interaction between pubertal stage and cortisol, as well as the three-way interaction of cortisol, pubertal stage, and stressful events did not predict depressive symptoms at 18 months, after controlling for baseline depressive symptoms.

[c] Cortisol is measured in nmol/L.

[d] The same analysis was repeated using CAR AUCi (area under the curve with respect to the increase) method. Consistent with the results of CAR, CAR AUCi did not predict depressive symptoms at 18 months. After controlling for the baseline covariates, the interaction between CAR AUCi and stressful events significantly predicted depressive symptoms at 18 months ($\beta = -.17$, $p < .05$).

(1SD below the mean) predicts the steepest increase in depressive symptoms. However, the effect is reversed at low levels of stress. That is, heightened CAR or greater daily cortisol output (1SD above the mean) is associated with more depressive symptoms. As presented in Figure 1A, the increase in depressive symptoms associated with blunted CAR is 1.5 times the increase in depressive symptoms associated with heightened CAR under the same changes in stress. The effect size is slightly larger for AUCg. When the same amount of stress increases, the increase in depressive symptoms associated with less daily cortisol output doubles the increase in symptoms associated with greater daily cortisol output.

Discussion

Two key findings emerged from the present study. First, consistent with the current literature [2–6,8], stressful events were strongly associated with depressive symptoms. Second, baseline diurnal cortisol interacted with later stressful events to predict subsequent depressive symptoms. Specifically, less daily cortisol output (smaller AUCg) in adolescent girls was associated with susceptibility to depressive symptoms when experiencing high levels of stressful events. Findings for CAR, which reflects a slightly different process than overall daily output, were more nuanced, with blunted CAR also predicting depression in the context of high levels of stress, but the reverse being true at low levels of stress. Taken together, the present findings provide support for the diathesis-stress framework in which blunted CAR and less daily cortisol output may reflect an HPA-related diathesis for depression, especially at high levels of stress. Blunted CAR and less daily cortisol output do not appear to be associated with depression at low levels of stress, and in fact may be associated with less depression, which to our knowledge has not been reported previously.

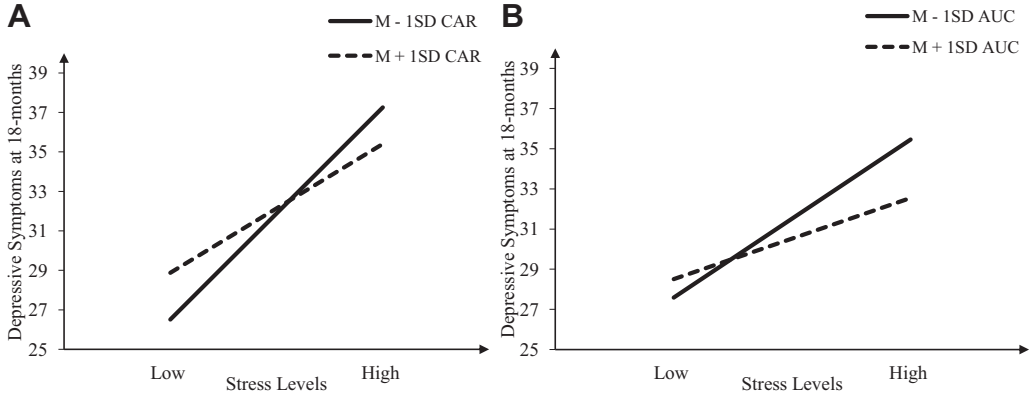

Figure 1. Illustration of the interaction between baseline diurnal cortisol and intervening stressful events in predicting depression symptoms at 18 months. (A) The interaction of CAR and stressful events; the slopes for the lines representing "M − 1SD CAR" and "M + 1SD CAR" are .34 and .21, respectively. (B) The interaction of AUCg and stressful events; the slopes for the lines representing "M − 1SD AUC" and "M + 1SD AUC" are .25 and .13, respectively.

Given that CAR and AUCg have a slightly different interaction patterns with stressful events, CAR and AUCg may index separate aspects of HPA axis activity governing the etiology of MDD during early adolescence. Indeed, CAR and AUCg reflect different aspects of daily cortisol circulation and have different sensitivity to stressful experience [8,17,32,33]. Specifically, CAR may be a unique component of the HPA axis, representing its response to awakening, and is less likely to be influenced by stressors throughout the day [32,33]. AUCg, on the other hand, reflects daily total cortisol circulation and may be more sensitive to stressors throughout the day [8]. As such, one would expect more cortisol being released (greater AUCg) within the body when stress is high [8,34]. In the present study, such elevation of cortisol was not observed. Instead, results showed that less cortisol was released in the context of high stress. This lack of cortisol elevation when it is supposed to be high suggests a lack of biological capacity in response to stressful events, which may contribute to development of depressive symptoms [10,34].

The present study found that blunted CAR and less daily cortisol output interacted with stressful events to prospectively predict depressive symptoms. This direction is opposite to those from previous findings in this area [8,15]. Two potential possibilities may explain this difference. The first possibility is the differences in pubertal development of the samples. The present sample included girls sampled from within a narrow age range, whereas previous studies included girls from late childhood to early adolescence (i.e., ages 9–14 years) [8] or female and male adolescents in late adolescence (i.e., mean age was 17.5 years) [15]. Youth at different pubertal stages may differ in their HPA axis functioning [35]. Such differences in the HPA axis functioning may further be associated with their ability to regulate negative emotion associated with the stressful events [35]. Colich et al. [35] have found that blunted cortisol reactivity to a laboratory-based stressor task predicted MDD onset in adolescent girls in early puberty. However, the effect was reversed for girls in the later pubertal stages, with elevated cortisol reactivity predicting MDD onset [35]. Given the narrow range of ages in the present study, we did not have power to test whether pubertal stage was indeed responsible for the direction of effects. The second possibility is that previous studies have sampled their cohorts from populations subjected to relatively low levels of stress [8,15]. Indeed, our results indicate that whether blunted CAR or less daily cortisol output worsening depression or improving symptomology may depend on the levels of stress.

The precise mechanism for this diathesis (e.g., smaller AUCg when stress is high) remains unclear. The HPA axis is characterized by several negative feedback loops to balance appropriate adaptation to stress and maintain homeostasis [10,34]. These negative feedback loops are informed by molecular, neurochemical, and environmental events, all of which may be the source of vulnerability reflected in low levels of cortisol. At the molecular level, increased sensitivity of glucocorticoid receptors (GRs) could potentially enhance the negative feedback loop within the HPA axis [10,34,36]. In the face of stress, cortisol is released as a biological defensive [34]. The amount of cortisol being released is generally detected by the negative feedback mechanism, in which GRs in the hippocampal region of the brain inhibit further activity of the HPA axis [10,34,36]. GRs play an important role of assuring cortisol levels within the body come back to normal levels once stress is removed [10,34,36]. It is possible that with increased sensitivity of GRs, the negative feedback mechanism starts to respond to cortisol release earlier than it should, leading to a prolonged inhibition of the activity of the HPA axis, and consequently, a greater suppression of cortisol (e.g., smaller AUCg) [36].

At the neurochemical level, sex hormones, which are rapidly changing during this period of development, affect the activity of negative feedback loop within the HPA axis [37,38]. Indeed, evidence from animal studies has shown a direct association between estrogens and HPA axis regulation in female rats [38]. Human studies have further revealed a positive association between the feedback sensitivity of the HPA axis and estrogen in females [38].

Finally, at the environmental level, other psychological factors might also be associated with enhanced negative feedback loop [39]. For example, individuals with a history of trauma exposure at young age have shown enhanced feedback inhibition within the HPA axis [37,39].

In addition, the blunted cortisol levels might reflect low levels of hormones released from other parts within the HPA axis. In the face of stress, hormones are released in a cascade manner within the HPA axis [10,36,38,39]. Cortisol is the last hormone being released within the HPA axis [10,38,39], and therefore, other hormones in the HPA axis will influence the amount of cortisol being released [10,38,39]. For example, adrenocorticotropic hormone is a hormone released from the anterior pituitary and then acts on the adrenal cortex to initiate the release of cortisol in humans [10,38]. If adrenocorticotropic hormone is released at relatively low levels, consequently, the amount of cortisol being released may not be enough compared with the normal amount that one's body needs to properly "defend" stress. Thus, it is important for future studies to examine predictive effects of the interaction between other hormones released within the HPA axis and stressful events in early adolescence.

The present study had several limitations. First, the present study examined the interaction effect of diurnal cortisol and stressful life events in female adolescents. Given the sex differences in the activity of the HPA axis, it is possible that results may differ when examining male adolescents. Second, the sample was recruited from the community, which enhances generalizability of our findings to the broader population but such samples are likely to experience less severe depressive symptoms on average than depressed youth recruited from clinics or other treatment-seeking populations. Replication with a population characterized by more severe depressive symptoms is warranted to evaluate the translational utility of diurnal cortisol. Third, given that the present sample included adolescent girls with a narrow age range, the study may be underpowered to detect the effect of a three-way interaction among diurnal cortisol, stressful events, and pubertal stages. To further understand the role of pubertal stages in etiology of depression, it is important to examine this three-way interaction in a sample selected based on different stages of pubertal development. Fourth, the present study relies on self-report of waking time. As such, we were not able to verify the self-reported waking time with an objective measure (e.g., actigraphy). Finally, we did not assess stress on the day of the sampling period per se. Such stressors may contribute to the day-to-day variability of cortisol and, as nuisance effects, may have weakened the magnitude of our observed effects.

In a large sample of adolescent girls, blunted CAR or less daily cortisol output combined with high burden of stressful life events prospectively predicted self-reported depressive symptoms, an important prognostic indicator for MDD onset in

adolescence [13]. The study highlights that blunted CAR and less daily cortisol output in adolescent girls are associated with susceptibility to depression.

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